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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/531,855	BERKEL ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims **1-13 and 16-22** are pending and presently under examination with respect to elected invention.

Specification

Foreign priority date for the invention, applied under 35 USC 119 (a)-(d) for the application number European Patent Office (EPO) 02079328.7 dated 10/17/2003 is granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims **1-19** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

The above claims are directed to C1-inhibitor that is changed with regard to its plasma circulatory half-life by modification of O-linked carbohydrate moieties.

The scope of the invention as claimed encompasses C1 inhibitor in or derived from any and all sources (plants, animals, mammals) that is modified under any conditions on its O-linked carbohydrate moieties (in vivo, ex vivo or in vitro) by any process (that occurs by naturally or induced gene mutations or epigenetic processes) that changes its plasma circulatory half life of said inhibitor in any fashion (up or down).

The specification only provides guidance and/or evidences regarding a modification of recombinant human C1 inhibitor (rhC1INH) isolated from milk of a transgenic rabbit wherein the inhibitor protein was scialylated in vitro using scialylating

enzymes ST3GalII alone (Example 1) or using both ST3GalII and ST3Gal I (Example 2) and their pharmacokinetic analysis by intravenous injection into rats (Example 3) wherein the injected modified protein exhibited increased half life. Further an in vitro modification of rhC1INH, by removal of non-sialylated O-glycans using a recombinant endo-α-N-Acetylgalactosaminidase enzyme (example 4) has also been described.

Besides in vitro modification of rhC1INH protein and its increased pharmacokinetics in a rat, the specification fails to disclose C1 inhibitor from any other source that is being modulated by modification as broadly claimed. Further it does not disclose specific examples of the claimed C1 inhibitor that is directly modified (sialylated) in vivo and which leads to its increased half-life in plasma circulation. Further specification fails to provide results of changed half-life of C1inhibitor molecules that have been partially or fully deglycosylated of the O-linked carbohydrate moieties.

Given the paucity in the art regarding the claimed induction of modification C1 inhibitor in vivo it is incumbent upon the applicant to describe the same and in sufficient number of examples to support the full breadth and scope of the claims. In the absence of adequate description commensurate with the scope and the breadth of the claims one of ordinary skill in the art would conclude that the inventor(s), at the time the application was filed, was not in possession of the broadly claimed invention. Claiming all divergent species that achieve a result as contemplated by the application without defining the means and/or uses will do so not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably

conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

At the best the specification teaches a recombinant human C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties in vitro using enzymes ST3Gal I and/or ST3GalII wherein the intravenously injected said modified protein exhibited increased half-life. Besides in vitro modified rhC1INH protein, the specification fails to disclose any modified C1 inhibitor molecules inhibitor that has been induced modified directly in vivo in order to increase said inhibitor plasma circulatory half-life.

Claims 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using an C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties in vitro and intravenously injecting the same to provide C1 inhibitor with increased half-life in plasma circulation, does not enable a method of increasing half-life of C1 inhibitor existing in vivo by direct modification or by using any other method including gene transfer or genetherapy as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level

of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope of the invention encompass modification of C1 inhibitor in vitro to increase its plasma half-life and further encompass providing C1 inhibitor modification directly in vivo by recombinant gene expression for enzymes that modify the O-glycosylated carbohydrate moieties. The latter thus encompasses gene therapy of humans. However applicant does not describe specific examples of any enzyme therapy or gene therapy for increasing the half-life of C1 inhibitor in vivo in any organism. In the absence of enabled and/or representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the number of claimed species nucleic acid species, sites of delivery and disease treatments completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability. Examiner, having read the instant specification broadly in the light of the Art, finds that such is not the case and hence concludes that the instant application does not reasonably provide enablement for the full breadth and scope of the claims and would have required undue experimentation for a skilled artisan to make and **use** the full scope of the methods as claimed.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the

art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

Guidance of the Specification and the Existence of Working Examples: With respect to invention instant specification only provides guidance and/or evidences regarding use of an a method of using an C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties in vitro and intravenously injecting the same to provide C1 inhibitor with an increased half-life in plasma circulation. However, specification does not describe any enabled examples of a method of increasing half-life of C1 inhibitor existing in vivo by it direct modification on O-glycosylated moieties either by scialylation or by deglycosylation using any methods including genetherapy and/or protein therapy as broadly claimed. Further the applicants do not indicate in the claim what such a therapy is for. Given the state of the art regarding these therapeutic methods coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods of treating all heart diseases as claimed.

State of the Art, the Predictability of the Art: At about the effective filing date of the present application art is unpredictable with regard to methods of gene transfers in vivo using both viral and non-viral vectors, as has been claimed in the instant invention, art is still unpredictable with regard to efficacy, specificity and safety. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). In addition there exists an unpredictability about the degree to which a foreign gene or vector would interfere with cellular genetic material as observed in treatment of X-SCID patients " These serious adverse events presented as a leukemia-like syndrome were surprising since the risk of insertional oncogenesis was considered to be negligible based on previous trials and on the perceived, though not universally accepted, notion of random retroviral integration" (Goncalves, Bioessays, 2005, 27: 506-517, p. 514, col.2, 1st ¶).

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo effects of claimed gene transfers for modifying O-glycosylation of C1 inhibitor in a subject. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enabled use of a method for safe treatment of a condition due to reduced half-life of C1 inhibitor and in sufficient number of examples as around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of using C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties in vitro and intravenously injecting the same to provide C1 inhibitor with increased half-life in plasma circulation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 and 16-18 are rejected under 35 USC 103 (a) as being unpatentable over Paulson et al (1998, WO 98/31826), Shoenberger et al (1992, FEBS 314;430-434), Wolf et al., (2001, protein expression and purification 22:414-421) and in view of Glaser et al (WO 92/03149).

The above claims are directed to C1-inhibitor that is changed with regard to its plasma circulatory half-life by modification of an O-linked carbohydrate.

Regarding claims 1-6 and Paulson teaches increasing plasma circulatory half life of therapeutic proteins including C proteins and other proteins that have been produced recombinantly by modifying both N- and O-glycosylation moieties (Abstract, p.2, 3rd

paragraph) by scialylation (p.2, 4th paragraph brdging p.3). Regarding claims 7-9 Paulson teaches use of one or more enzymes including ST3 gal I, ST3 Gal III etc., (p.3, 2 and 3rd paragraph and p.18, Examples). Regarding claim 10-12 Paulson teaches various recombinant glycoproteins that are modified in vitro sialylation (p.7, 2nd, 3rd and 4th paragraph bridging p.8, and p.25). However, Paulson does not teach C1-INH and the importance of O-glycosylation.

Schoenberger teaches C1 inhibitor and recombinant C1 inhibitor and the characterization of the carbohydrate moieties and removal of sialic acids from native molecules (p.431, col.2) and the characterization of desialylated C1-inhibitor (p.432, 2nd paragraph) and further considered to see whether the carbohydrate part of C-1 inhibitor influences the inhibition mechanism of the inhibitor (p.433, col.2, 2nd paragraph)

Wolf teaches regarding production and purification of recombinant C1 inhibitor and the various glycosylations levels of C1INH (p.415, col.1, 2nd paragraph). Wolf further teaches the differences between native and recombinant molecules in terms of their glycosylation and the importance of reduced O-glycosyaltion in hereditary diseases involving (p.419, col.2, 2nd paragraph). He further indicates engineered glycosylation pathways to obtain recombinant inhibitor (rC1INH) for clinical evaluation (p.420, col.1).

Glaser teaches a method of treating a thrombotic disease using therapeutic proteins like C protein that are modified in sugar residues of the O-linked glycosylation domain and encompassing modification by deletion of sugar moieties enzymatically (p.4, 1st paragraph).

Thus it would have been obvious for one of ordinary skill in the art to incorporate into compositions and methods of C1 inhibitor preparation for therapeutic purposes to incorporate scialylation of the recombinantly produced C1 inhibitor to increase its half-life in plasma circulation and use it for therapeutic purpose. One skilled in the art would be motivated to do so for treating disease connected with reduced C1 inhibitory activity by providing recombinant protein that has been modified to increase its plasma

circulatory half life by scialylating carbohydrate moieties because of the teachings of Paulson, Schoenberger, Wolf, and Glaser as above.

Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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9/12/06